Vitamin D Deficiency ,diabetic nephropathy

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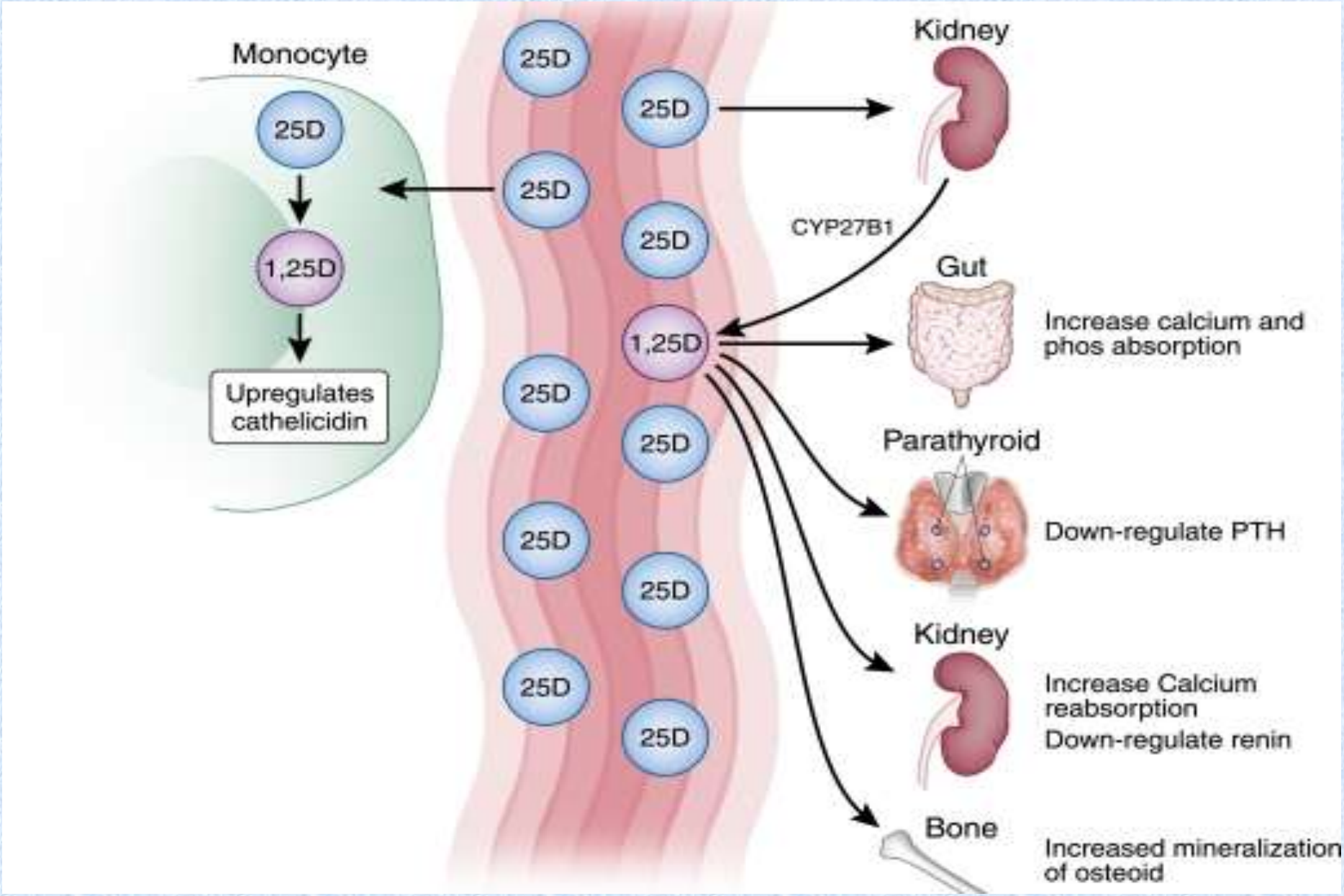
- ***Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations***
- ***It enables normal mineralization of bone.***
- ***It prevents hypocalcemic tetany.***
- ***It is also needed for bone growth and bone remodeling by osteoblasts and osteoclasts .***

, the most important compounds in this group are vitamin D3 (cholecalciferol) and

vitamin D2(ergocalciferol)

Vitamin D obtained from sun exposure, food, and supplements is biologically inert and must undergo two hydroxylations in the body for activation. The first occurs in **the liver** and converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. The second occurs **primarily in the kidney a**nd forms the physiologically active 1,25-dihydroxyvitamin D [1,25(OH)2D], also known as calcitriol



Physiology of vitamin D in the body.

- Serum concentration of 25(OH)D is the best indicator of vitamin D status.
- its half-life of 15 days.
- **A level of 20 nanograms/milliliter to 50 ng/mL is considered adequate for healthy people.**
- **A level less than 12 ng/mL indicates vitamin D deficiency**

Table 1: Serum 25-Hydroxyvitamin D [25(OH)D] Concentrations and Health*

nmol/L**	ng/ml	Health status
<30	<12	Associated with vitamin D **deficiency**, leading to rickets in infants and children and osteomalacia in adults
30–50	12–20	Generally considered **inadequate for bone and overall health in healthy individuals**
≥50	≥20	Generally considered **adequate** for bone and overall health in healthy individuals
>125	>50	Emerging evidence links potential adverse effects to such **high levels,** particularly >150 nmol/L (>60 ng/mL)

Table2: Recommended Dietary Allowances (RDAs) for Vitamin D

Age	Male	Female	Pregnancy	Lactation
0–12 months*	400 IU (10 mcg)	400 IU (10 mcg)		
1–13 years	600 IU (15 mcg)	600 IU (15 mcg)		
14–18 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
19–50 years	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)	600 IU (15 mcg)
51–70 years	600 IU (15 mcg)	600 IU (15 mcg)		
>70 years	800 IU (20 mcg)	800 IU (20 mcg)		

Vitamin D sources

- synthesis of vitamin D (specifically cholecalciferol) in the skin is the major natural sources of the vitamin.
- Dermal synthesis of vitmain D from cholesterol is dependent on sun exposure (specifically UV-B radiation).

Few foods are naturally

good sources of vitamin D.

- fatty fish including salmon, sardines, cod, tuna and halibut.
- breakfast cereals and milk, are fortified with vitamin D. Milk must contain at least 100 IU of vitamin D per cup.

Table 3: Selected Food Sources of Vitamin D

Food	IUs per serving*	Percent DV**
Cod liver oil, 1 tablespoon	1,360	340
Swordfish, cooked, 3 ounces	566	142
Salmon (sockeye), cooked, 3 ounces	447	112
Tuna fish, canned in water, drained, 3 ounces	154	39
Orange juice fortified with vitamin D, 1 cup (check product labels, as amount of added vitamin D varies)	137	34
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	115-124	29-31
Yogurt, fortified with 20% of the DV for vitamin D, 6 ounces (more heavily fortified yogurts provide more of the DV)	80	20
Margarine, fortified, 1 tablespoon	60	15
Sardines, canned in oil, drained, 2 sardines	46	12
Liver, beef, cooked, 3 ounces	42	11
Egg, 1 large (vitamin D is found in yolk)	41	10
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75-1 cup (more heavily fortified cereals might provide more of the DV)	40	10
Cheese, Swiss, 1 ounce	6	2

Causes of vitamin deficiency

- dietary inadequacy
- impaired absorption and use
- increased requirement
- increased excretion.

A vitamin D deficiency can occur when usual intake is lower than recommended levels over time, exposure to sunlight is limited, the kidneys cannot convert 25(OH)D to its active form, or absorption of vitamin D from the digestive tract is inadequate

Groups at Risk of Vitamin D Inadequacy

- Older adults
- People with limited sun exposure
- people with dark skin
- People with inflammatory bowel disease and other conditions causing fat malabsorption: including some forms of liver disease, cystic fibrosis, celiac disease, and Crohn's disease, as well as ulcerative colitis when the terminal ileum is inflamed
- People who are obese or who have undergone gastric bypass surgery

Vitamin D not only bone regulator

- It has become clear that insufficient 1,25(OH)2D may contribute to a wide variety of nonbone health problems.
- The vitamin D receptor (VDR) is present in virtually all cells.
- 1,25(OH)2D complexes with the VDR and coreceptors to regulate transcription
- Through this mechanism, 1,25(OH)2D regulates cell proliferation and differentiation, immune cell function, and a number of tissue-specific processes.

Antiproteinuric effect of Vitamin D

- Vitamin D has an important regulatory effect on the renin-angiotensin-aldosterone system, playing a central role in the regulation of proteinuria.
- The Vitamin D concentration was significantly negatively correlated with urinary albumin excretion rate.
- The inform**ation available is insufficient to advise the use of native vitamin D or VDR activators as renoprotective antiproteinuric drugs beyond the experimental level**

Vitamin D Deficiency: Consequence or Cause of CKD?

- In **CKD, renal production of (1,25(OH)2D) from (25(OH)D) is markedly reduced.**
- **Many factors could account for the low levels of 25 (OH) vitamin D observed in patients with CKD including :**

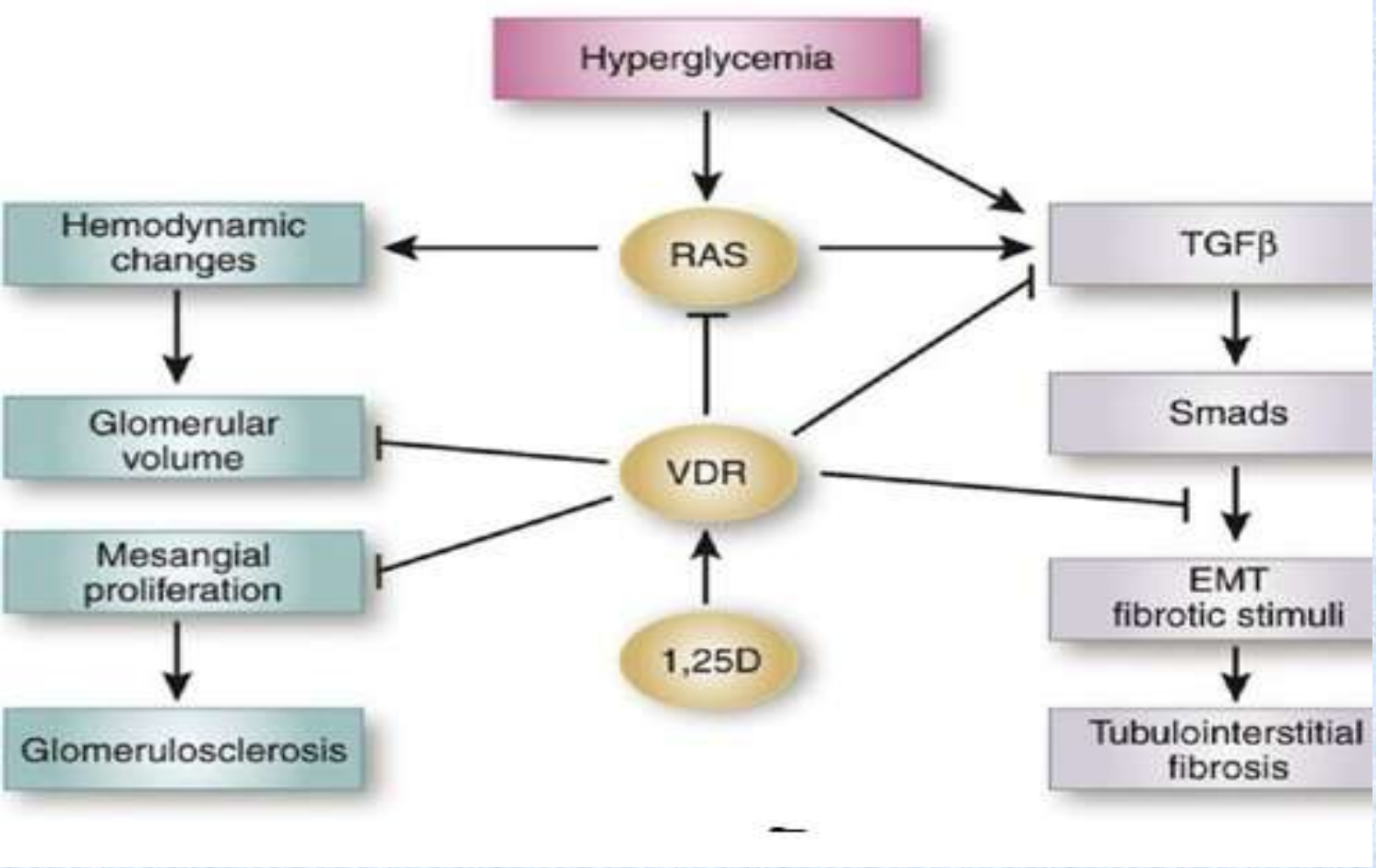
1- loss of vitamin D–binding protein in urine.

2-ineffective synthesis in skin on exposure to ultraviolet B radiation.

3- reduced nutritional intake .

4-the progressive increase in fibroblast growth factor levels .

- **Hyperglycemia increases abundance and translocalization of protein kinase Calpha (PKC alpha) in glomerular cells and, most prominently, in capillaries**.
- **Angiotensin II is also known to stimulate PKC.**
- **An important effect of PKC stimulation is an increase in transforming growth factor-beta (TGF-beta**), resulting in increased capillary permeability and fibrogenic activity.



Proposed effects of active vitamin D metabolites on development of diabetic nephropathy

Hyperglycemia stimulates the intrarenal renin–angiotensin system (RAS) and formation of transforming growth factor-beta (TGF-beta) and other cytokines as well as proteinuria. TGF-beta induces tubular epithelial-to-mesenchymal transition and stimulation of profibrotic signals. Increased activity of the RAS induces hemodynamic changes in the glomerulus followed by increased glomerular volume, mesangial proliferation, and podocyte injury. Active vitamin D metabolites bind to the vitamin D receptor (VDR) and inhibit stimulation of the RAS as well as podocyte and mesangial-cell proliferation. In addition, active vitamin D counterbalances fibrogenesis by inhibiting TGF-beta indirectly via the activation of hepatocyte growth factor. In consequence, active vitamin D metabolites reduce glomerulosclerosis and tubulointerstitial fibrosis

Vitamin D deficiency , diabetic nephropathy

- **25 (OH) vitamin D deficiency is independently associated with a higher risk of the composite outcome in patients with type II diabetic nephropathy.**
- **25(OH)D <15 ng/ml was associated with (>50% increase in serum creatinine, ESRD, or death)**
- **these studies suggest a large range of potential renal benefit from vitamin D supplementation.**

the most important **limitation** of some study is its observational design, which can lead to confounding. **Physical inactivity, diets low in dairy and oily fish, adiposity, heavy proteinuria, and other unfavorable health habits and conditions lead to low 25(OH)D concentrations. It could be these characteristics, rather than insufficient 25(OH)D itself, that adversely affect the kidney**. Observational studies of 25(OH)D are therefore insufficient on their own to change practice.

- Type 2 diabetic patients with mild kidney impairment, vitamin D deficiency was shown to be strongly associated with a higher prevalence of manifest cardiovascular disease when compared with normal vitamin D status .
- 25 (OH) vitamin D deficiency is associated with accelerated progression of CKD in patients with DN.
- Patients with established DN are expected to have lower 25 (OH) vitamin D levels than patients with CKD of other causes but a similar GFR .

Logistic regression analysis demonstrated that vitamin D deficiency was associated with nephropathy **even after the adjustment for age, gender, hypertension, dyslipidemia, smoking status, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers**

On the other hand, other study was not able to demonstrate an association between baseline levels of 25(OH)D3 and development of microvascular complications in type 1 diabetic patients.

A rapid decline in renal function is defined as a sustained decline in eGFR of > 5 mL/min per 1.73 m per year.

Many factors contributing to a rapid decline in renal function include ethnic/genetic and demographic causes, smoking habits, increased glycated hemoglobin levels, obesity, albuminuria, anemia, low serum magnesium levels, high serum phosphate levels, vitamin D deficiency, elevated systolic blood pressure, pulse pressure, brachial-ankle pulse wave velocity values, retinopathy, and cardiac autonomic neuropathy.

the early detection of diabetic subjects who are at risk of a rapid decline in renal function in order to develop a more **aggressive** approach to renal and cardiovascular **protection**.

Vitamin D supplementation in kidney disease

- Correction of deficient/insufficient 25-hydroxy vitamin D levels in CKD patients is justified based on evidence for local 1-alpha hydroxylase activity in nonrenal target tissues, a modest reduction in PTH levels with nonactivated vitamin D therapy, absence of toxicity, and low cost.
- Nutritional vitamin D repletion can be accomplished using either vitamin D2 or vitamin D3.

- Increasing evidence suggests that current recommendations for vitamin D intake are inadequate, particularly for populations at risk for suboptimal vitamin D status, such as those with diabetes, kidney disease
- Some studies recommended dose 1200 iu cholecalciferol daily for 3m , or ergocalciferol 50,000iu\w for 8-12 w then followed by 800 IU cholecalciferol \d , or 50,000 IU ergocalciferol \month

- While others suggest that vitamin D supplementation (2,000 IU/day and 40,000 IU/month) for six months will result in significantly improved overall vitamin D status and improved markers of bone health in adult patients with diabetic nephropathy.
- The need for RCTs assessing higher doses of vitamin D3 supplementation at varying frequencies of administration and its impact on bone health in adults with diabetes and chronic kidney disease are needed

- Activated oral vitamin D agents are calcitriol,and paricalcitol. Starting dosages for these agents are 0.25 mcg daily for calcitriol, 1 mcg daily for paricalcitol.
- Treatment with an activated vitamin D agent should target a PTH level <70 pg/mL for stage III CKD patients or <110 for stage IV CKD patients, and requires monitoring of serum calcium and phosphate levels.

If a person has a high blood level of phosphorus or calcium, the physician will often choose not to treat the high PTH with activated vitamin D because there is an increased risk of calcium-phosphorus deposits in the soft tissues

- Various studies **suggest reduced podocyte injury and less mesangial proliferation with the administration of active vitamin D metabolites**. Reduced glomerular and tubulointerstitial alterations are accompanied by reduced proteinuria in experimental diabetic nephropathy and other experimental kidney disease.
- **These findings all suggest that vitamin D deficiency should be avoided in diabetic and nondiabetic chronic kidney disease**.

- it remains premature to measure 25(OH)D concentrations or prescribe vitamin D–related therapies for the purpose of improving kidney or other nonbone outcomes.
- Instead, vitamin D–related therapies should be guided by our knowledge of how CKD affects the vitamin D endocrine system and bone health.
- In the future, the table may turn, with focus directed instead on the effect of the vitamin D endocrine system on CKD.

Summary

- The prevalence of nephropathy was higher in the patients with vitamin D deficiency than those with normal vitamin D concentration
- vitamin D deficiency should be avoided in diabetic and nondiabetic chronic kidney disease
- Reduced proteinuria with administration of active vitamin D
- RCTs assessing higher doses of vitamin D3 supplementation in adults with diabetes and chronic kidney disease are needed
- It remains premature to measure 25(OH)D concentrations or prescribe vitamin D–related therapies for the purpose of improving kidney outcome


Thank You.